NOVEDADES en EAS 2010

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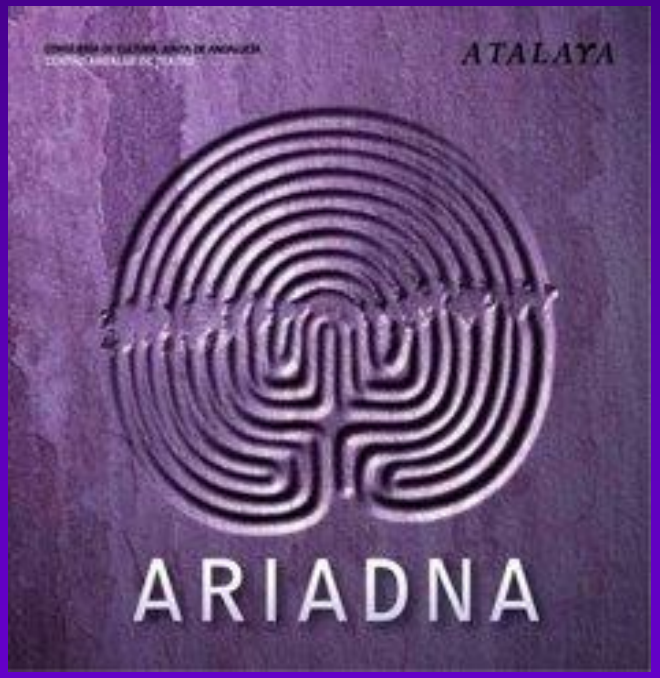
Bases genéticas



Association of HLA Class II Genes with Systemic Sclerosis in Spanish Patients

CARMEN P. SIMEÓN, VICENT FONOLLOSA, CARLES TOLOSA, EDUARD PALOU, ALBERT SELVA, ROSER SOLANS, LLUIS ARMADANS, ESTEFANIA MORENO, SARA MARSAL, and MIQUEL VILARDELL

ABSTRACT. ***Objective.*** To examine the role of HLA-DRB1 and HLA-DQB1 alleles in the susceptibility to systemic sclerosis (SSc) and its clinical expression in a Spanish population.

Methods. One hundred Spanish Caucasian patients with SSc and 130 controls were studied. Molecular HLA-DRB1 and HLA-DQB1 typing was performed by polymerase chain reaction (PCR) sequence-based typing and PCR sequence-specific oligonucleotide.

Results. HLA-DRB1*11 was associated with genetic susceptibility to SSc, whereas HLA-DRB1*07 (HLA-DRB1*0701) showed a protective effect. A significant increase in the frequency of the DRB1*1104 allele was observed in patients with anti-topoisomerase I autoantibodies (anti-Topo I) while HLA-DRB1*01 and HLA-DQB1*05 alleles were significantly increased in patients with anti-centromere antibodies (ACA). The HLA-DRB1*11 allele was more frequent in patients with pulmonary fibrosis; however, no significant association with any HLA-DRB1 or DQB1 alleles was identifie

Conclus h patients. Some alleles are n h certain SSc-specific autoantib 1 2009; doi:10.3899/jrheum.0

some studies have also shown a relationship between PF and HLA-DR3, our data showed that no other alleles were associated with either PF or PAH in SSc[8].

This is the first study to examine the role of HLA-DRB1 and HLA-DQB1 alleles in the genetic susceptibility to SSc and its clinical and serological expression in a Spanish Caucasian SSc population. Our data support the hypothesis

J Rheumatol 2009;36:2.733.36

nature genetics

Genome-wide association study of systemic sclerosis identifies *CD247* as a new susceptibility locus

Timothy R D J Radstake[1,37], Olga Gorlova[2,37], Blanca Rueda[3,37], Jose-Ezequiel Martin[3,37], Behrooz Z Alizadeh[4], Rogelio Palomino-Morales[3], Marieke J Coenen[5], Madelon C Vonk[1], Alexandre E Voskuyl[6], Annemie J Scheurwegh[7], Jasper C Broen[1], Piet L C M van Riel[1], Ruben van 't Slot[4], Annet Italiaander[4], Roel A Ophoff[4,8], Gabriela Riemekasten[9], Nico Hunzelmann[10], Carmen P Simeon[11], Norberto Ortego-Centeno[12], Miguel A González-Gay[13], María F González-Escribano[14], Spanish Scleroderma Group[36], Paolo Airo[15], Jaap van Laar[16], Ariane Herrick[17], Jane Worthington[17], Roger Hesselstrand[18], Vanessa Smith[19], Filip de Keyser[19], Fredric Houssiau[20], Meng May Chee[21], R Madhok[21], Paul Shiels[21], Rene Westhovens[22], Alexander Kreuter[23], Hans Kiener[24], Elfride de Baere[25], Torsten Witte[26], Leonid Padykov[27], Lars Klareskog[27], Lorenzo Beretta[28], Rafaella Scorza[28], Benedicte A Lie[29], Anna-Maria Hoffman-Vold[30], P Carreira[31], J Varga[32], M Hinchcliff[32], Peter Gregersen[32], Annette T Lee[32], Jun Ying[2], Younghun Han[2], Shih-Feng Weng[2], Christopher I Amos[2], Fredrick M Wigley[33], Laura Hummers[33], J Lee Nelson[34], Sandeep K Agarwal[35], Shervin Assassi[35], Pravitt Gourh[35], Filemon K Tan[35], Bobby P C Koeleman[4,37], Frank C Arnett[35,37], Javier Martin[3,37] & Maureen D Mayes[35,37]

Nat Genet 2010;42:426-9

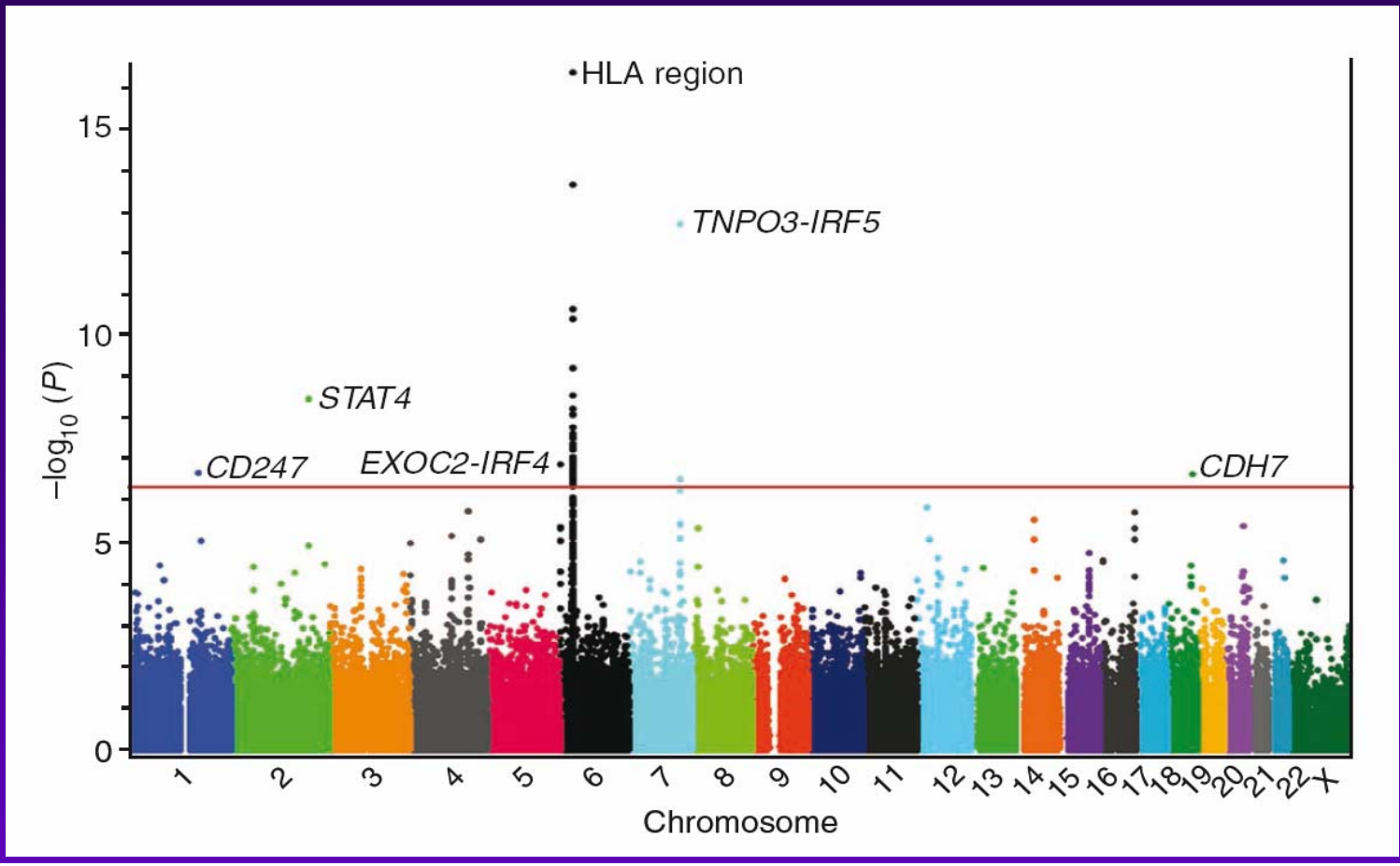
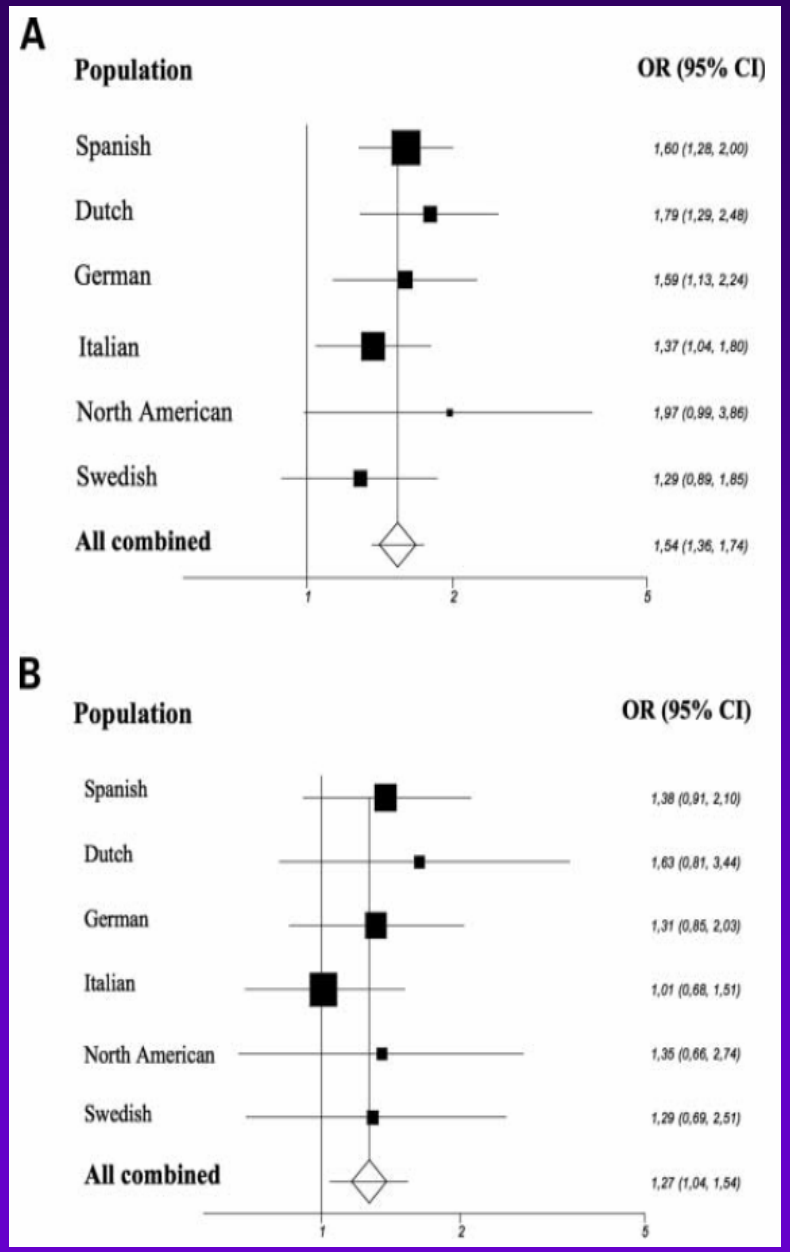


Table 1 Loci showing the strongest association signal with SSc susceptibility outside the MHC region

Chr.	Gene	SNP	Location	BP	Minor allele	MAF (case/control)	GC-corrected *P* value	PC-corrected *P* value	OR (95% CI)
7q32	*TNPO3-IRF5*	rs10488631	Downstream	128,381,419	C	0.145/1.102	1.86×10^{-13}	3.84×10^{-14}	1.50 (1.35–1.67)
		rs12537284	Intergenic	128,505,142	A	0.162/0.129	2.74×10^{-7}	1.49×10^{-7}	1.30 (1.18–1.44)
		rs4728142	Upstream	128,361,203	A	0.494/0.445	5.21×10^{-7}	1.81×10^{-7}	1.21 (1.12–1.29)
2q32	*STAT4*	rs3821236	Intronic	191,611,003	A	0.247/0.202	3.37×10^{-9}	3.93×10^{-9}	1.30 (1.19–1.41)
1q22–23	*CD247*	rs2056626	Intronic	165,687,049	G	0.370/0.421	2.09×10^{-7}	3.27×10^{-7}	0.82 (0.76–0.88)
18q22	*CDH7*	rs10515998	Intergenic	61,521,202	G	0.062/0.040	2.25×10^{-7}	1.01×10^{-7}	1.53 (1.31–1.79)
6p25	*EXOC2-IRF4*	rs4959270	Intronic	402,748	A	0.445/0.494	1.23×10^{-7}	9.06×10^{-8}	0.82 (0.77–0.88)

Chr., chromosome; BP, base pairs; MAF, minor allele frequency; GC, genomic control; PC, ; OR, odds ratio.



Human Molecular Genetics, 2009, Vol. 18, No. ? **1–7**
doi:10.1093/hmg/ddp119
Advance Access published on xxx

The *STAT4* gene influences the genetic predisposition to systemic sclerosis phenotype

B. Rueda[1], J. Broen[2], C. Simeon[4], R. Hesselstrand[5], B. Diaz[6], H. Sanchez[6], N. Ortego-Centeno[7], G. Riemekasten[8], V. Fonollosa[4], M.C. Vonk[2], F.H.J. van den Hoogen[9], J. Sanchez-Román[10], M.A. Aguirre-Zamorano[11], R. García-Portales[12], A. Pros[13], M.T. Camps[14], M.A. Gonzalez-Gay[15], M.J.H. Coenen[3], P. Airo[16], L. Beretta[17], R. Scorza[17], J. van Laar[18], M.F. Gonzalez-Escribano[19], J.L. Nelson[20], T.R.D.J. Radstake[2] and J. Martin[1,*]

RESULTS

STAT4 is associated with limited cutaneous SSc in the Spanish population

BANK1 Is a Genetic Risk Factor for Diffuse Cutaneous Systemic Sclerosis and Has Additive Effects With *IRF5* and *STAT4*

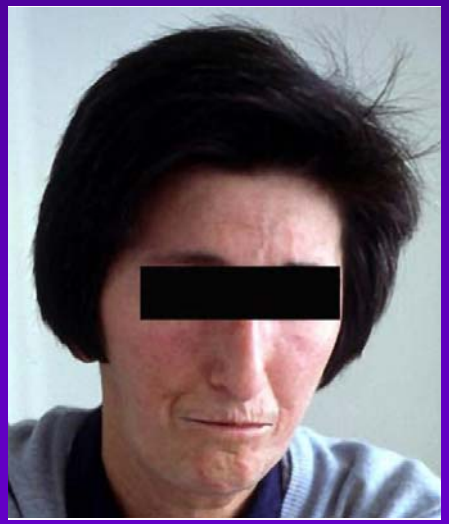
Diudé P et al. *Arthritis and Rheumatism*. 2009;60:3.447-454

Conclusion. Our results establish *BANK1* as a new SSc genetic susceptibility factor and show that *BANK1*, *IRF5*, and *STAT4* act with additive effects.

BANK1 functional variants are associated with susceptibility to diffuse systemic sclerosis in Caucasians

B Rueda, P Gourh, J Broen, S K Agarwal, C P Simeón, N Ortego-Centeno, M C Vonk, M Coenen, G Riemekasten, N Hunzelmann, R Hesselstrand, F K Tan, J D Reveille, S Assasi, F J Garcia-Hernandez, P Carreira, M Camps, A Fernandez-Nebro, P Garcia de la Peña, T Nearney, D Hilda, M A Gónzalez-Gay, P Airo, L Beretta, R Scorza, T RDJ Radstake, M Mayes, F C Arnett and J Martin

Ann Rheum Dis 2010;69:700-705



Conclusion: Our results suggest that *BANK1* gene confers susceptibility to SSc in general, and specifically to the dcSSc and anti-topoisomerase-I antibody subsets.

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Evolución clínica
Supervivencia

Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study

S.I. NIHTYANOVA[1], E.C. TANG[1], J.G. COGHLAN[2], A.U. WELLS[3], C.M. BLACK[1] and C.P. DENTON[1]

QJMed. 2010;103:109-115

Table 1 Demographic and clinical characteristics of the contemporary and historical cohorts

Characteristic	Subset					
Onset	DcSSc			LcSSc		
	1990–93	2000–03	*P*-value	1990–93	2000–03	*P*-value
Number of patients	74	130		160	156	
Female gender, *n* (%)	61 (82)	97 (75)	NS	140 (88)	129 (83)	NS
Age at onset, years (mean ± SD)	45 ± 14	47 ± 15	NS	49 ± 13	52 ± 13	NS
Follow-up, months (mean ± SD)	110 ± 65	61 ± 22	<0.001	147 ± 58	70 ± 21	<0.001
Follow-up <5 years, *n* (%)	2 (3)	21 (16)	0.003	7 (4)	24 (15)	0.001
ANAs, *n* (%)						
ACA	1 (1)	2 (2)	NS	64 (40)	59 (38)	NS
ATA	11 (15)	43 (33)	0.005	27 (17)	25 (16)	NS
ARA	8 (11)	36 (28)	0.005	6 (4)	5 (3)	NS
Non-defined ANA	24 (32)	26 (20)	0.047	18 (11)	26 (17)	NS
Other	14 (19)	20 (15)	NS	28 (18)	39 (25)	NS
ANA negative	2 (3)	3 (2)	NS	7 (4)	9 (6)	NS
Not known	16 (22)	6 (5)	<0.001	16 (10)	2 (1)	<0.001
Patients analysed for ENAs	41 (55)	122 (93)	<0.001	132 (83)	152 (97)	<0.001
Kaplan–Meier estimation of event cumulative incidence at 5 years, *n* (%)						
Death	23 (31)	19 (16)	0.018	14 (9)	10 (7)	NS
PF	5 (7)	44 (38)	<0.001	5 (3)	24 (16)	<0.001
Pulmonary hypertension	1 (1)	7 (7)	NS	1 (1)	11 (8)	0.002
Renal crisis	13 (19)	18 (14)	NS	0 (0)	4 (3)	0.042
Cardiac involvement	1 (1)	5 (4)	NS	2 (1)	1 (1)	NS

Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study

S.I. NIHTYANOVA[1], E.C. TANG[1], J.G. COGHLAN[2], A.U. WELLS[3], C.M. BLACK[1] and C.P. DENTON[1]

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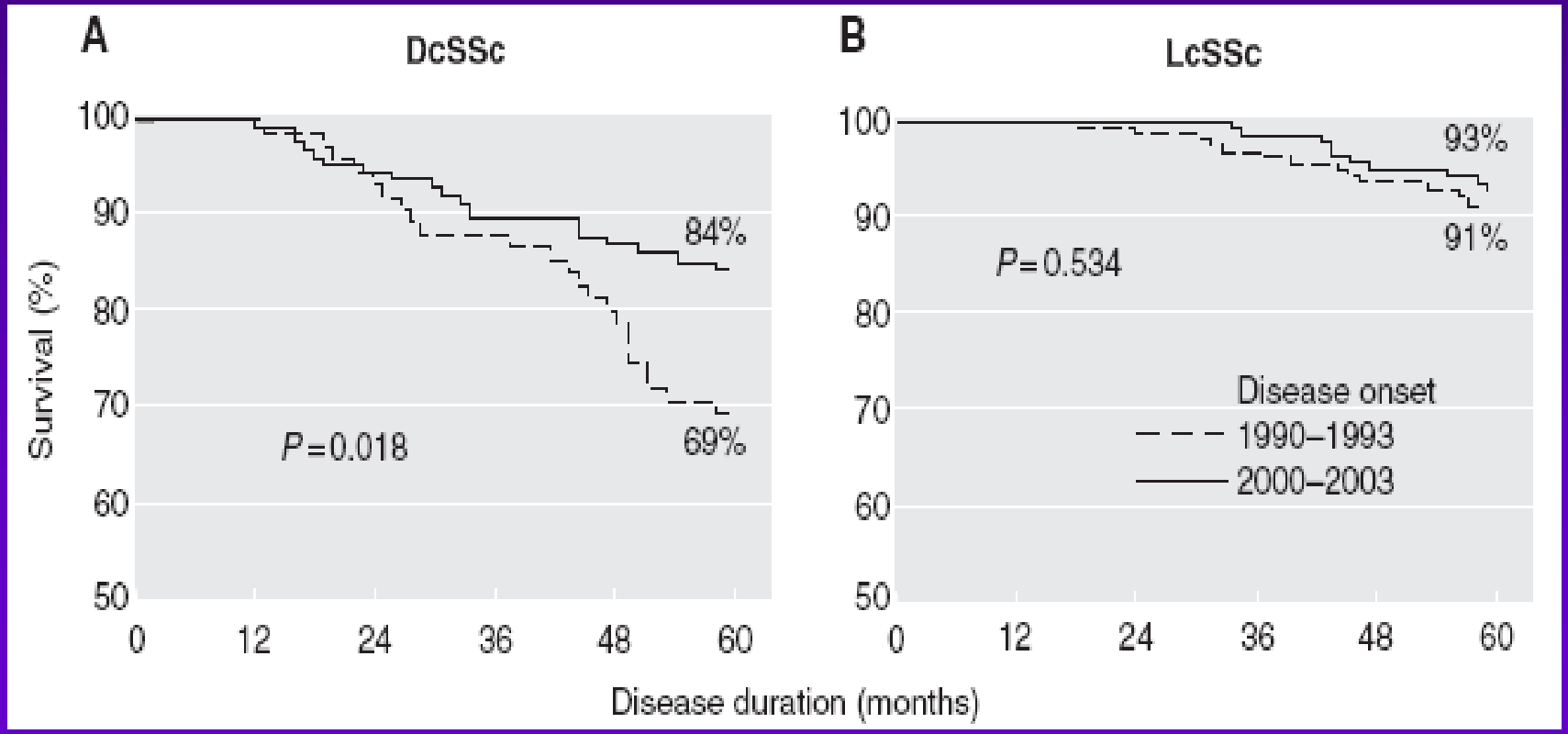

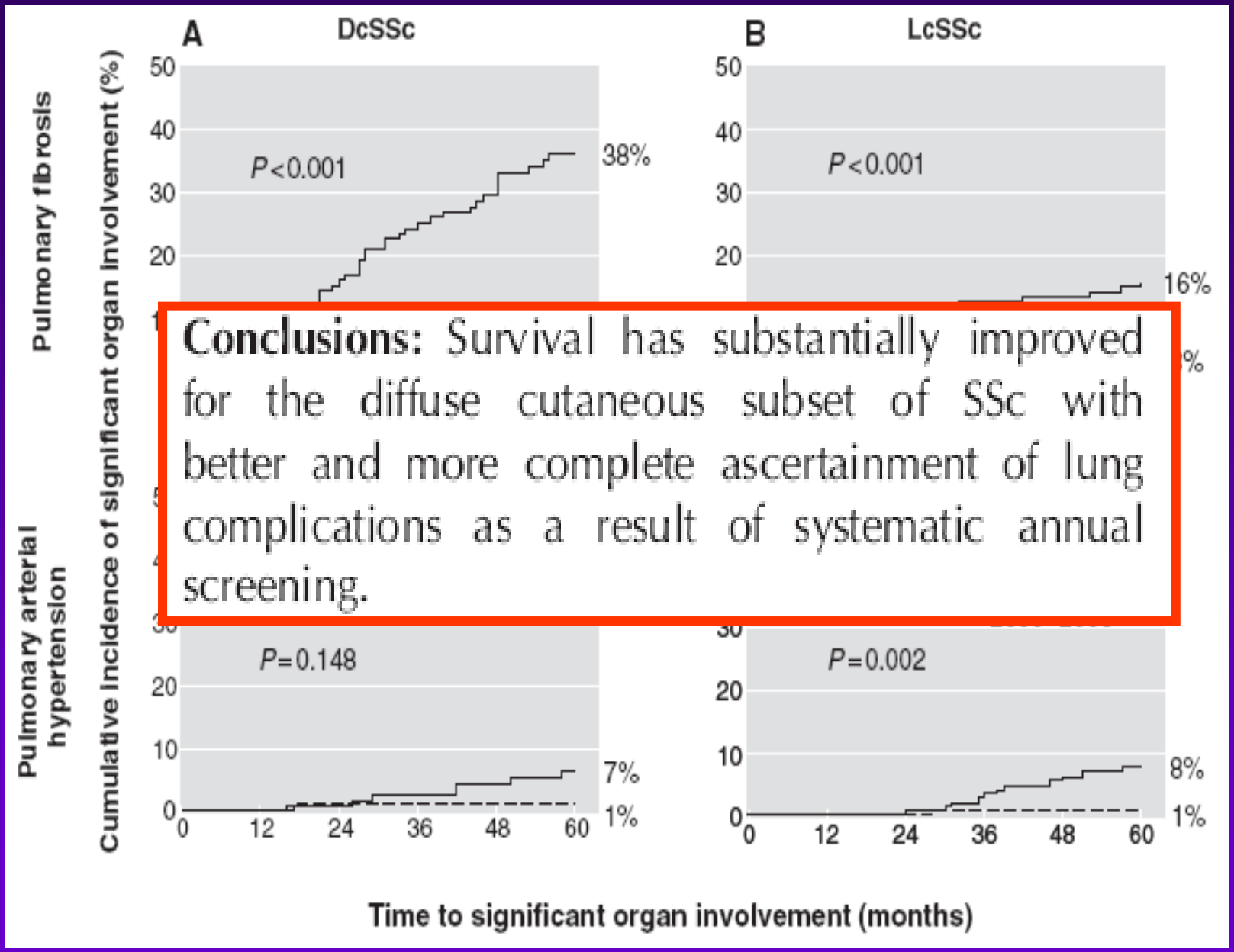

Conclusions: Survival has substantially improved for the diffuse cutaneous subset of SSc with better and more complete ascertainment of lung complications as a result of systematic annual screening.

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HIPERTENSIÓN ARTERIAL PULMONAR

Systemic Sclerosis-associated Pulmonary Arterial Hypertension

Jérôme Le Pavec[1,2], Marc Humbert[2], Luc Mouthon[3], and Paul M. Hassoun[1]

SCOPE OF THE PROBLEM
- Prevalence and incidence
- Risk factors
- Survival

ROLE OF INFLAMMATION AND AUTOIMMUNITY
- Inflammatory Cells
- Vascular changes (Remodeling)
- Autoantibodies in SSc-PAH
- Candidate genes

THE IMPACT OF COMORBITIES
- Age
- Myocardial involvement
- Musculoskeletal involvement
- Pulmonary fibrosis
- Pulmonary venoocclusive disease

LACK OF RELIABILITY OF CURRENT EVALUATION TOOLS
- The 6-Minute Walk Test
- Righ heart Catheterization

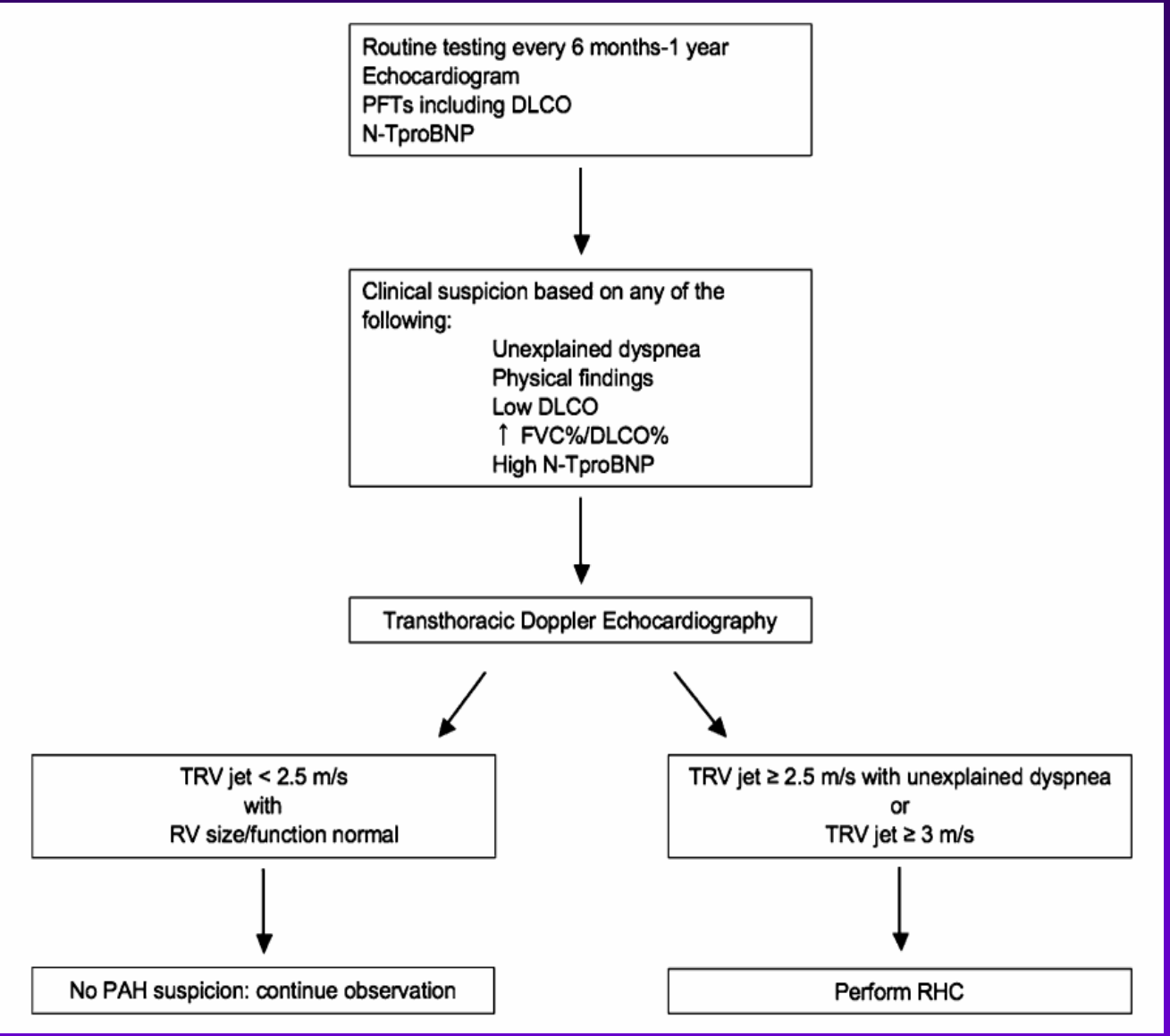
CURRENT MEDICAL THERAPIES FOR SSc-PAH

FUTURE DIRECTIONS FOR MEDICAL THERAPIES

FUTURES PERSPECTIVES
- Early diagnosis
- Assesing Markers of Severity
- Evaluation of the RV

Am J Respir Crit Care Med. 2010;181:1.285-93

FUTURE PERSPECTIVES. Early Diagnosis



FUTURE PERSPECTIVES. Assessing markers of severitiy

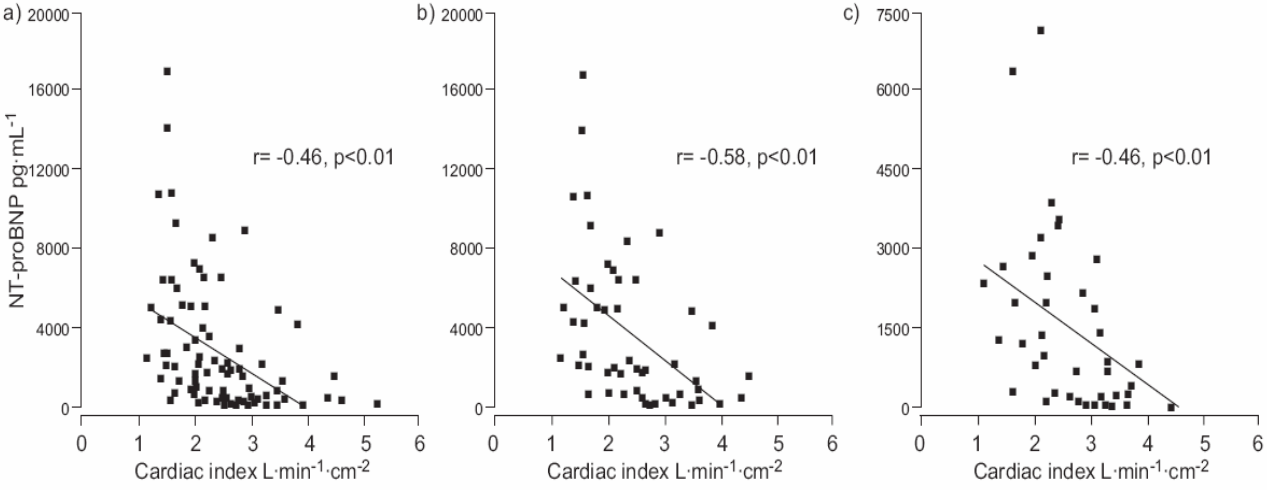
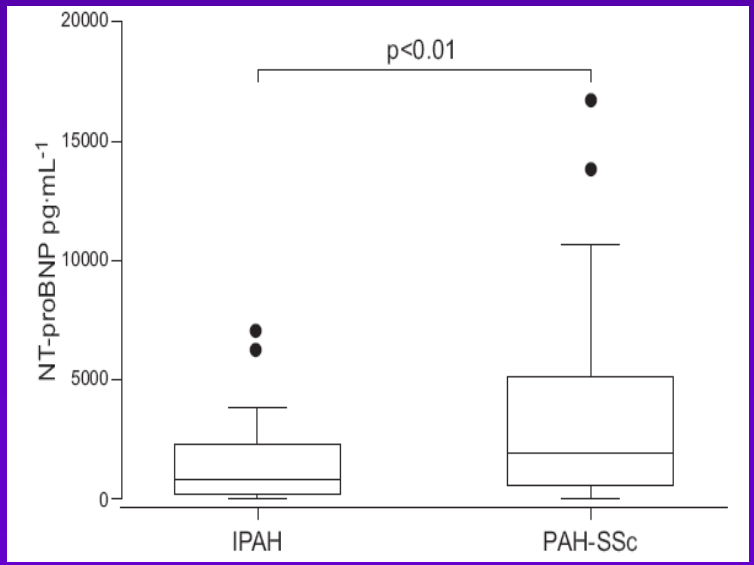


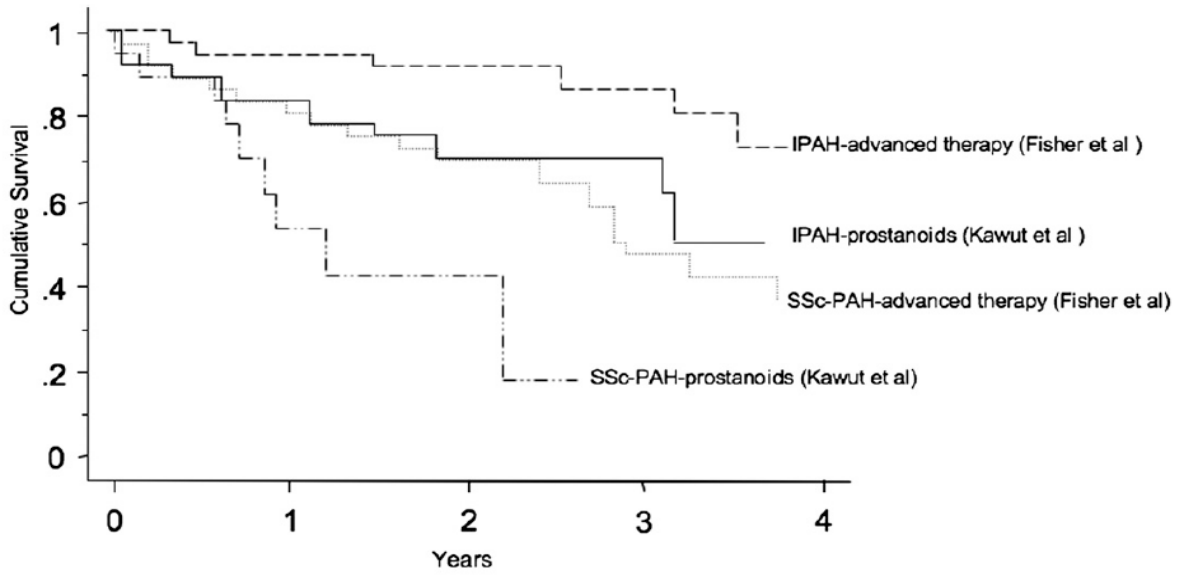
FIGURE 2. Correlations between N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac index in a) the overall cohort, b) pulmonary arterial hypertension related to systemic scleroderma patients and c) idiopathic pulmonary arterial hypertension patients.



In conclusion, in this cohort of patients with PAH, NT-proBNP levels were significantly higher in PAH-SSc subjects compared to IPAH subjects despite similar haemodynamics, suggesting differences in response to cardiac load. Furthermore, NT-proBNP was a strong predictor of survival only in the PAH-SSc group, further emphasising the role of this noninvasive marker in the evaluation of patients with PAH-SSc. Although the

Mathai SC et al. Eur Respr J. 2010;35:95-104

FUTURE PERSPECTIVES: Evaluation of the Right Ventricular



Studies	Kawut et al [6]		Fisher et al [4]	
Period of time	1997-2001		2000-2005	
Patients	IPAH n = 33	SSc-PAH n = 22	IPAH n = 41	SSc-PAH n = 50
First line PAH therapy	Prostanoïds		ERA, PDE5 inhibitors, or prostanoïds according to guidelines	
NYHA FC III-IV, %	-		77.5	64
mPAP, *mmHg*	52 ± 12	48 ± 10	54 ± 1.9	47 ± 1.5
CI, $L.min^{-1}.m^{-2}$	2.1 ± 0.62	2.2 ± 0.54	2.1 ± 0.1	2.2 ± 0.1
PVR, $dyn.s.cm^{-5}$	918 ± 433	755 ± 238	941 ± 88	855 ± 83

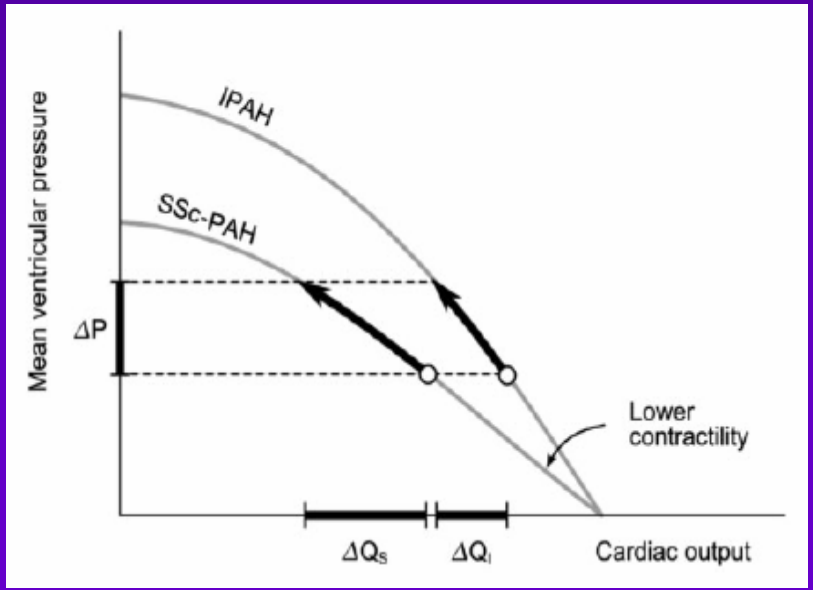
Table 2. Baseline right heart catheterization findings*

	IPAH (n = 41)	PAH-Scl (n = 50)	*P*
Right atrial pressure, mm Hg	10.1 ± 0.9	11.2 ± 0.7	0.36
Pulmonary artery systolic pressure, mm Hg	86.4 ± 2.9	75.6 ± 2.4	0.004
Pulmonary artery pressure, mm Hg	54.4 ± 1.9	46.6 ± 1.5	0.002
Pulmonary capillary wedge pressure, mm Hg	12.0 ± 0.8	11.4 ± 0.7	0.59
Cardiac index, liters/minute/m^2	2.1 ± 0.1	2.2 ± 0.1	0.19
Pulmonary vascular resistance index, Wood units	22.8 ± 1.8	17.5 ± 1.5	0.026

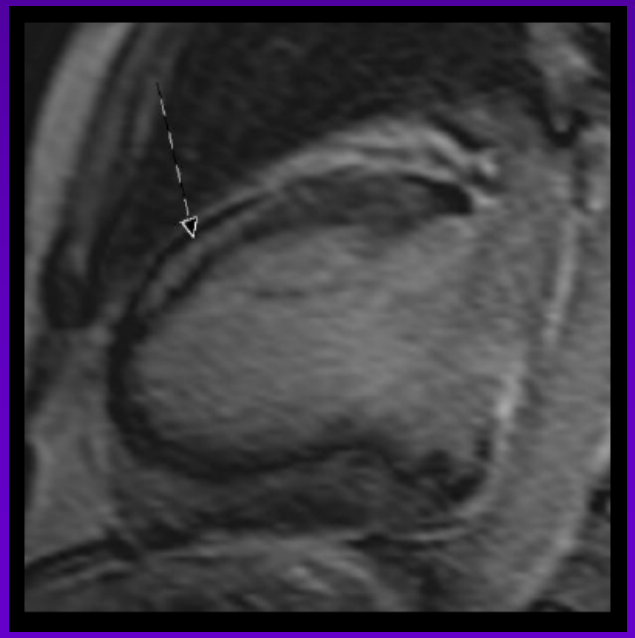
Fisher MR et al. *Arthritis Rheum*, 2006

Table 3. Baseline echocardiographic findings*

	IPAH (n = 38)	PAH-Scl (n = 49)	*P*
Right atrial dilation	31 (81.6)	36 (73.5)	0.37
Right ventricular dilation	34 (89.5)	39 (79.6)	0.21
Right ventricular hypertrophy	7 (18.4)	5 (10.2)	0.27
Left atrial diameter, mean ± SEM cm	3.3 ± 0.2	3.8 ± 0.1	0.004
Left atrial dilation	4 (10.5)	14 (28.6)	0.039
Left ventricular hypertrophy	5 (13.2)	17 (34.7)	0.022
Left ventricular ejection fraction, mean ± SEM	57.3 ± 1.6	55.7 ± 1.4	0.44
Diastolic dysfunction	5 (13.2)	16 (32.7)	0.035
Pericardial effusion	5 (13.2)	17 (34.7)	0.022



A Vonk Noordegraaf et al. *Rheumatology*, 2008



Hachulla AL et al. *Ann Rheum Dis*, 2009

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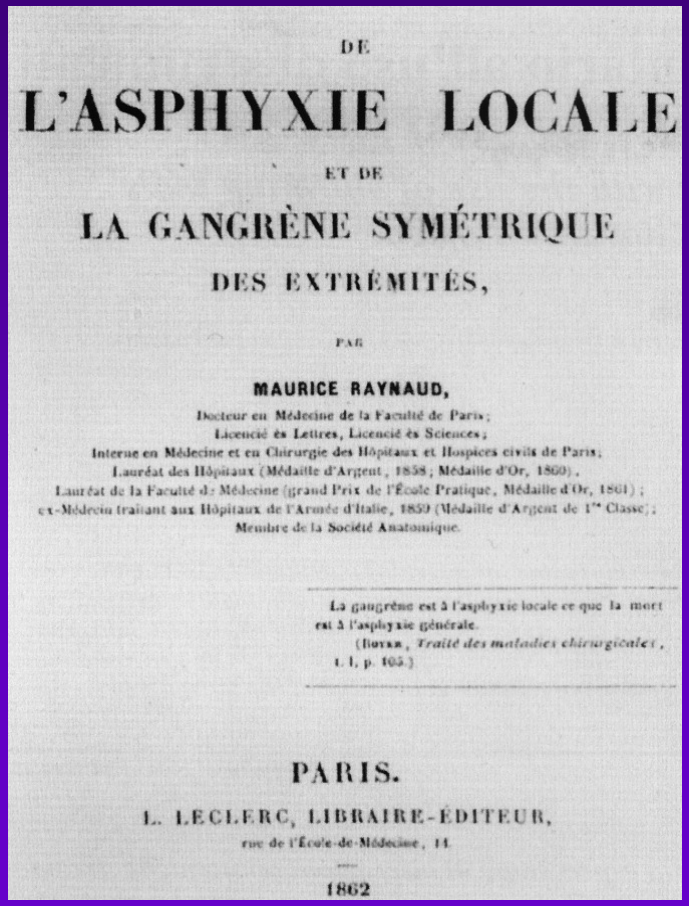
Diagnóstico



DE

L'ASPHYXIE LOCALE

ET DE

LA GANGRÈNE SYMÉTRIQUE

DES EXTRÉMITÉS,

PAR

MAURICE RAYNAUD,

Docteur en Médecine de la Faculté de Paris;
Licencié ès Lettres, Licencié ès Sciences;
Interne en Médecine et en Chirurgie des Hôpitaux et Hospices civils de Paris;
Lauréat des Hôpitaux (Médaille d'Argent, 1858; Médaille d'Or, 1860);
Lauréat de la Faculté de Médecine (grand Prix de l'École Pratique, Médaille d'Or, 1861);
ex-Médecin traitant aux Hôpitaux de l'Armée d'Italie, 1859 (Médaille d'Argent de 1re Classe);
Membre de la Société Anatomique.

La gangrène est à l'asphyxie locale ce que la mort est à l'asphyxie générale.
(Bichat, *Traité des maladies chirurgicales*, t. I, p. 105.)

PARIS.

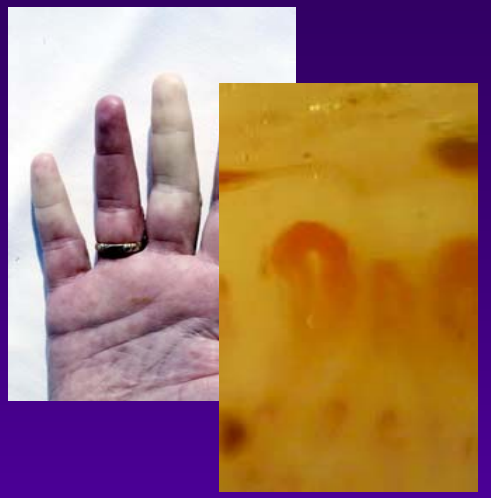
L. LECLERC, LIBRAIRE-ÉDITEUR,
rue de l'École-de-Médecine, 14.

1862

Prognostic Model Based on Nailfold Capillaroscopy for Identifying Raynaud's Phenomenon Patients at High Risk for the Development of a Scleroderma Spectrum Disorder

Ingegnoli F et al. Arthritis Rheum. 2008

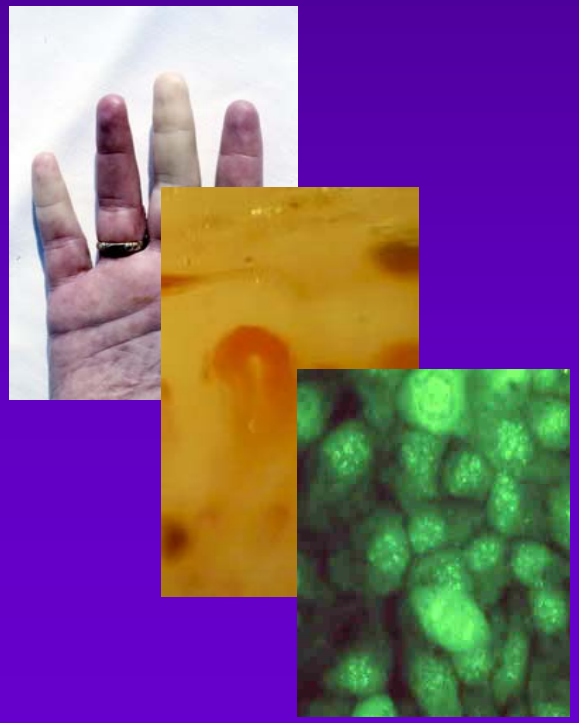
Conclusion. **Our prognostic capillaroscopic index identifies RP patients in whom the risk of developing SSDs is high. This model is a weighted combination of**



Autoantibodies and Microvascular Damage Are Independent Predictive Factors for the Progression of Raynaud's Phenomenon to Systemic Sclerosis

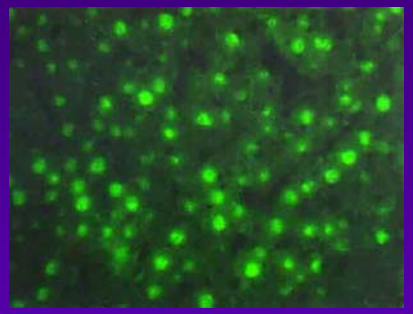
Koenig M et al. Arthritis and Rheumatism. 2008

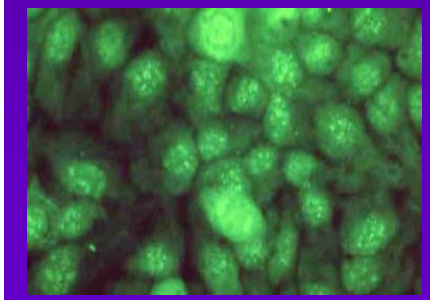
and type of capillary abnormalities. Abnormal findings on NCM at baseline together with an SSc-specific autoantibody indicate a very high probability of developing definite SSc, whereas their absence rules out this outcome.

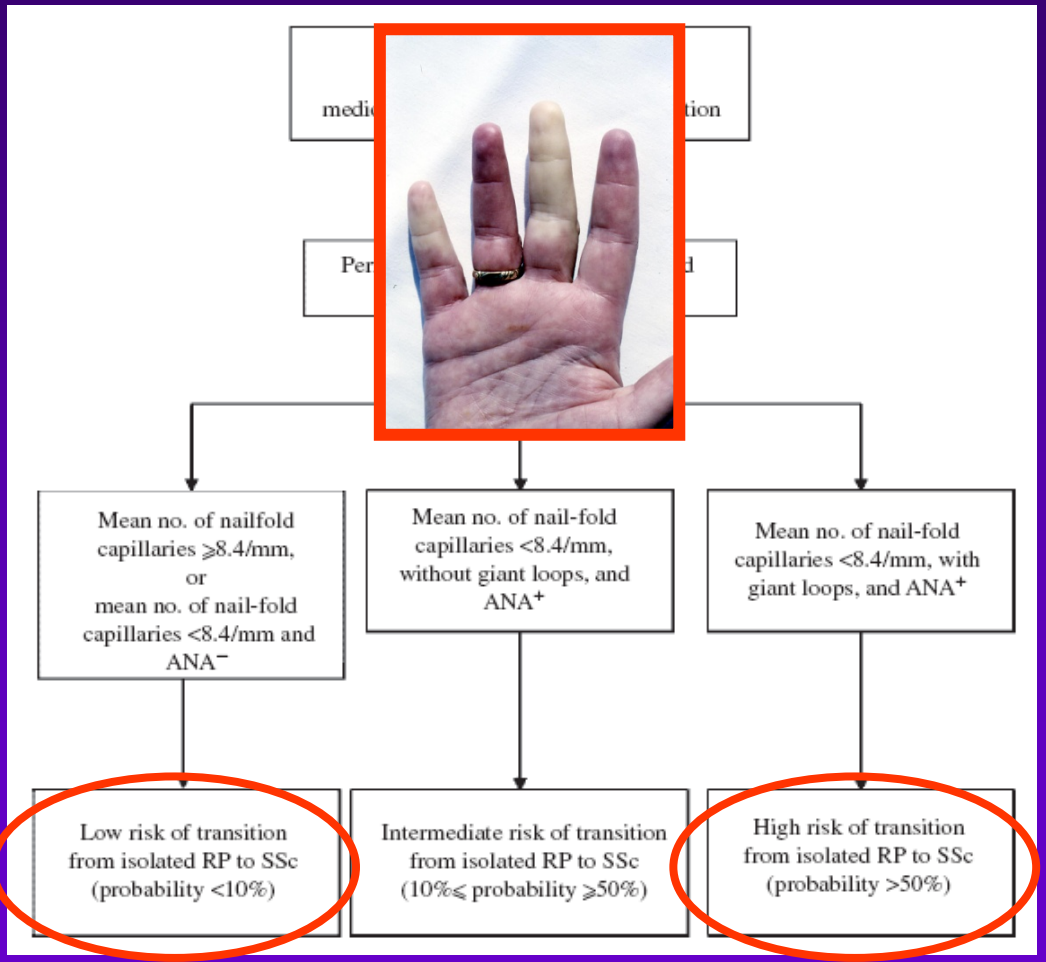


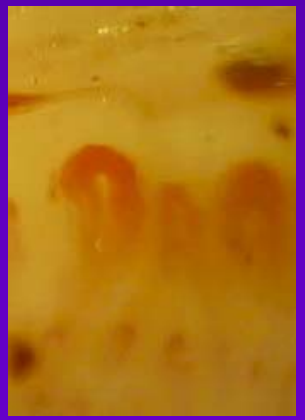
Improving outcome prediction of systemic sclerosis from isolated Raynaud's phenomenon: role of autoantibodies and nail-fold capillaroscopy

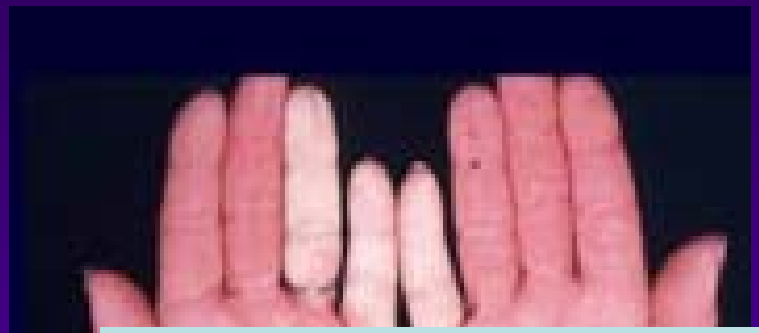
Ingegnoli F et al. *Rheumatology (Oxford) Jan 25, 2010*

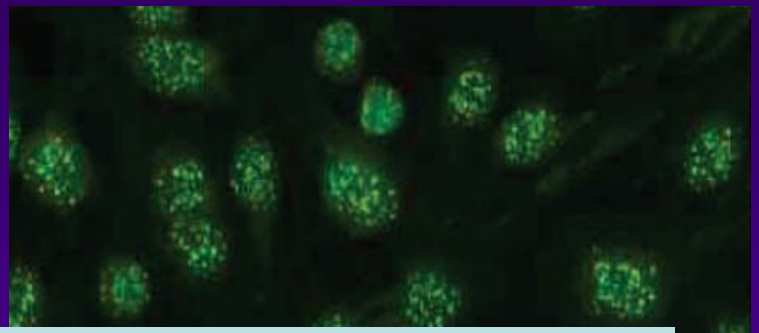












Pre- esclerodermia o
FASE INICIAL DE LA ESCLERODERMIA

Criterios diagnósticos/pronósticos

Nuevas perspectivas terapéuticas

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Tratamiento

Targeted therapy for systemic sclerosis: how close are we?

Manuel Ramos-Casals, Vicent Fonollosa-Pla, Pilar Brito-Zerón and Antoni Sisó-Almirall

Nat Rev Rheumtol. 2010;6:269-278

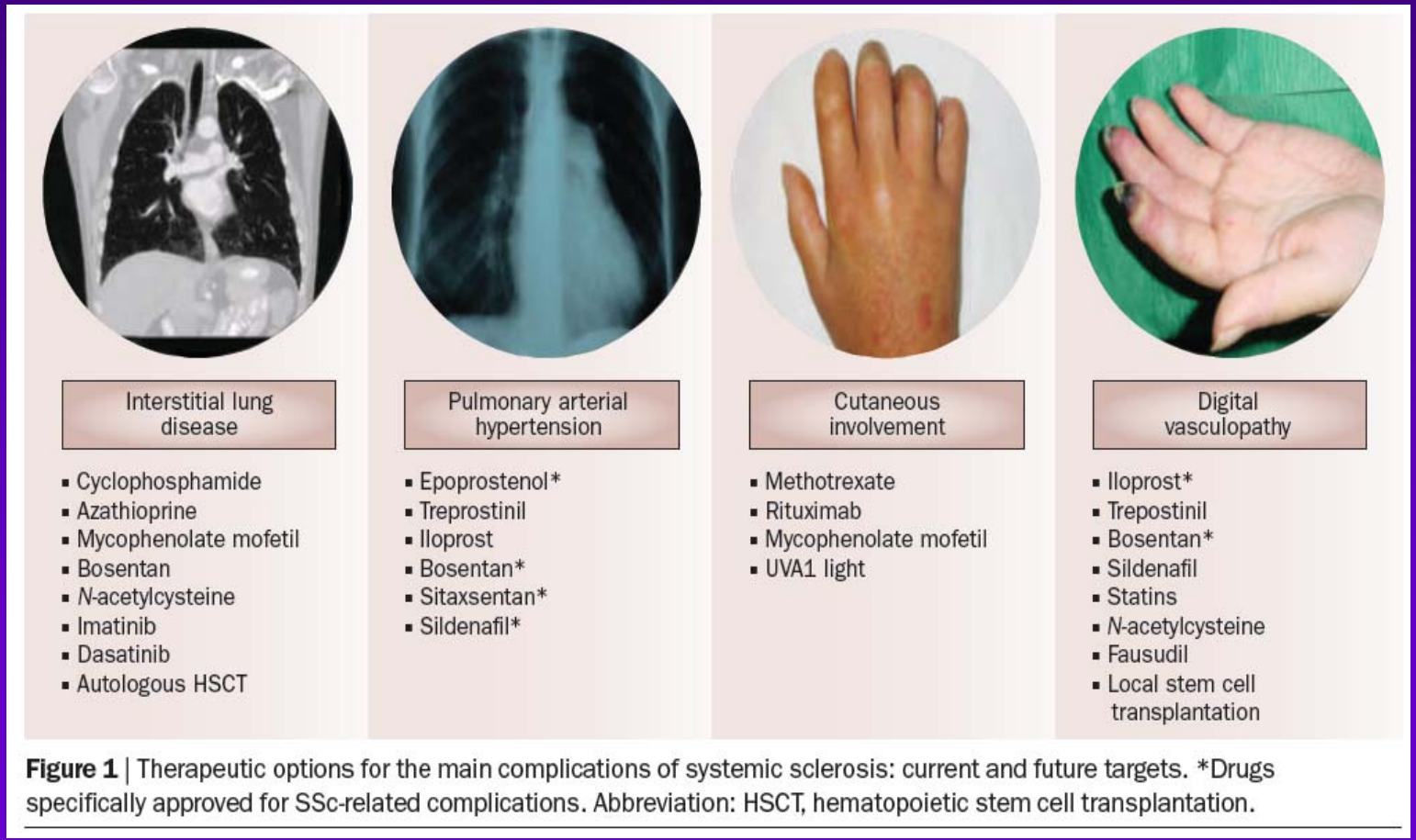

Figure 1 | Therapeutic options for the main complications of systemic sclerosis: current and future targets. *Drugs specifically approved for SSc-related complications. Abbreviation: HSCT, hematopoietic stem cell transplantation.